(1) a leader sequence; and

(2) a DNA sequence encoding hPTH comprising a functional signal sequence encoded by an amino-terminal amino acid sequence, the expression product of which can direct secretion in yeast, wherein the leader sequence and the hPTH sequence are operably linked;

(b) culturing said microorganism to allow expression of said DNA sequence encoding hPTH, thereby producing hPTH (1-84); and

(c) purifying the resultant hPTH (1-84) protein.

51. The composition of claim 50, wherein the signal sequence is encoded by the following amino acid sequence:

Met-Asn-Ile-Phe-Tyr-Ile-Phe-Leu-Phe-Leu-Ser-Phe-Val-Gln-Gly-Thr-Arg-Gly.--

REMARKS

Applicants respectfully request reconsideration and reexamination of this application.

I. REQUEST FOR ENTRY OF AMENDMENT AFTER FINAL REJECTION

It is acknowledged that the amendments to the claims are made after final rejection. This case was recently transferred to the undersigned for prosecution, after both options for requesting withdrawal of finality under § 1.129 had been exercised. As described in more detail below, after review of the Examiner's arguments made throughout the prosecution of this case, the newly submitted claims were drafted to add limitations addressing the Examiner's arguments, and to distinguish the claimed invention over the cited prior art. In addition, Applicants' are filing herewith a Terminal Disclaimer to overcome the obviousness-type double patenting rejection.

In sum, all of the claim amendments were made in response to comments or arguments previously presented by the Examiner. In particular, product-by-process claims 38, 41, 44, 48, and 50 were added to recite "essential elements" for expression of hPTH, in response to the Examiner's rejection of the claims under 35 U.S.C. § 112, second paragraph (page 2 of the Office Action dated June 3, 1998). In addition, claim 31 was amended and

claims 36 and 37 were added to recite a hPTH composition distinguishable from native hPTH, in response to the Examiner's rejection of the claims under §§ 102(b) and 103 (Office Action dated June 3, 1998, at pages 3-4).

Finally, it is courteously submitted that the claim amendments and the following arguments place the application in condition for allowance. For these reasons, and because the foregoing amendments to the claims do not introduce new matter, entry thereof by the Examiner is respectfully requested.

II. STATUS OF THE CLAIMS

Claims 31 and 36-51 are pending in the application, following entry of the Amendment. All of the pending claims are directed to human parathyroid hormone compositions, as elected by Applicants in a Response to a Restriction Requirement, dated June 6, 1995.

Claims 6-10, 12, 14, 16-20, 32, and 33-35, have been cancelled, without disclaimer or prejudice thereof, for the sole purpose of advancing the prosecution of this case. Applicants reserve the right to prosecute the subject matter of the cancelled claims is this or another application.

Amended claim 31 and new claims 36 and 37 are directed to a composition comprising human parathyroid hormone (hPTH) (1-84), wherein the hormone has a point mutation at amino acid 26 changing the amino acid from lysine (K26) to glutamine (Q26). The resultant hPTH is superior to wild-type hPHT in that it is resistant to degradation. *See e.g.*, page 17, lines 7-15, of the Application.

Claims 38-43 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism comprising the sequence for hPTH and, as a leader sequence, a modified sequence for *Saccharomyces* mating factor α1 (MFα1). For claims 38-40, the MFα1 sequence lacks the yeast STE13 recognition site, and for claims 41-43, the MFα1 sequence comprises only the first 19 amino acids of the sequence.

Claims 44-47 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism having a leader sequence and a modified hPTH sequence.

Claims 48-51 are directed to a composition comprising hPTH (1-84), wherein the hormone is made using a microorganism having a leader sequence and either an optimized consensus signal sequence or a functional signal sequence.

Exemplary support provided in the specification for the amended claim and the new claims is given in the following table.

CLAIMS	EXEMPLARY SUPPORT IN SPECIFICATION
31	Page 3, lines 25-27; page 17, lines 11-18; page 22, lines 3-27.
36	Page 20, lines 35-38.
37	Page 20, lines 36-38; page 21, line 36, through page 22, line 2.
38	Page 3, lines 27-30; page 14, lines 20-27; and page 35, line 6, through page 36, line 23.
39, 42	Page 3, lines 10-13; and original claim 10.
40, 43, 47	Page 7, lines 30-32; and page 5, lines 19-22.
41	Page 14, lines 31-35; and page 36, line 25, through page 37, line 35.
44	Page 19, lines 4-17; page 39, lines 7-24; page 37, line 36, through page 38, line 4.
45	Page 14, line 36, through page 15, line 11.
46	Page 6, lines 22-28; page 14, lines 15-20.
48	Page 23, line 30, through page 24, line 29.
49	Page 24, line 30, through page 25, line 36.
50	Page 24, lines 2-7; page 25, lines 3-6.
51	Page 25, line 37, through page 26, line 8.

Because the foregoing amendments do not introduce new matter, entry thereof by the Examiner is respectfully requested.

III. SUMMARY OF THE INVENTION

The present invention is directed to a compositions comprising recombinant hPTH. hPTH is an important regulator of calcium metabolism in mammals, and is also related to several mammalian diseases, such as milk fever, acute hypocalsemia, and otherwise pathologically altered blood calcium levels. *See* page 2, lines 15-19, of the Application. Through its action on target cells in bone and kidney tubuli, hPTH increases serum calcium and decreases serum phosphate, while opposite effects are found regarding urinary excretion of calcium and phosphate. *See* page 5, lines 27-31, of the Application. hPTH is useful, for

example, as a component of a diagnostic kit or as a therapeutic in human and veterinary medicine. *See* page 2, lines 20-22, of the Application.

Prior to the present invention, hPTH was commercially available only in very small quantities at high cost, partly because synthesis of the compound was difficult and complex. *See* page 1, lines 33-38, of the Application. Moreover, recombinant production of hPTH was hampered by the discovery that *E. coli* degrades human hPTH.

Applicants have overcome the problems of the prior art and discovered compositions of recombinant hPTH that can be made in high yield using microorganisms.

The present invention is directed to a composition comprising a modified recombinant hPTH, wherein the modified hPTH is degradation resistant (claims 31, 36, and 37). *See* page 15, lines 18-28, of the Application. The modified hPTH has a correct size, full immunological reactivity with two different specific hPTH antibodies, a correct N-terminal amino acid sequence, and comparable biological activity to the wild-type hPTH. *See* page 15, lines 31-38, of the Application.

In addition, the invention is directed to compositions comprising recombinant hPTH, wherein the hPTH is prepared in microbial cells (claims 38-51). The compositions are made by a process in which (1) the microorganism comprises a modified sequence for *Saccharomyces* MFα1 (claims 38-43); (2) the microorganism comprises a modified hPTH sequence (claims 44-47); and (3) the microorganism comprises either an optimized consensus signal sequence or a functional signal sequence (claims 48-51). *See e.g.,* page 14, lines 20-27 and 31-35; page 19, lines 4-17; page 23, line 30, through page 24, line 29; page 24, lines 2-7; page 24, line 30, through page 25, line 6; and page 35, line 6, through page 37, line 35, of the specification. Such compositions are superior to those known prior to the claimed invention. Compositions according to the claimed invention can be made in dramatically increased yields of, for example, 5- to 10-fold greater than the prior art. *See e.g.,* page 5, lines 6-12; page 14, lines 23-27; and page 17, lines 7-11, of the specification.

IV. THE OFFICE ACTION

A. Obviousness-Type Double Patenting Rejection

Claims 31-35 were rejected under the judicially created doctrine of obviousness-type double patenting as being allegedly unpatentable over claims 1 and 21-30 of commonly-assigned U.S. Patent No. 5,010,010. Office Action at page 2. Applicants respectfully traverse this ground for rejection.

While Applicants respectfully traverse this ground for rejection, filed herewith for the sole purpose of advancing prosecution is a Terminal Disclaimer for U.S. Patent No. 5,010,010 ("the '010 patent") disclaiming the portion of the term of any patent issuing on this application subsequent to the expiration date of the '010 patent.

B. Objections and Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 33-35 were rejected under 35 U.S.C. § 112, second paragraph, as being allegedly incomplete for omitting essential elements, such as a secretory leader sequence. Office Action at pages 2-3. Applicants respectfully traverse this ground for rejection.

While Applicants respectfully disagree with the Examiner's analysis, claims 38-51, which correspond to the subject matter of cancelled claims 33-35, have been drafted to recite compositions of hPTH made using microorganisms that comprise (1) a leader sequence and (2) a DNA sequence encoding hPTH, wherein the leader sequence and the hPTH sequence are operably linked. These amendments have been made for the sole purpose of advancing prosecution. Because Applicants' claims are definite, withdrawal of this ground for rejection is respectfully requested.

C. Rejections under 35 U.S.C. §§ 102(b) and/or 103

Claims 31 and 32 were rejected under 35 U.S.C. § 102(b) as being allegedly anticipated by or, in the alternative, under 35 U.S.C. § 103 as being allegedly obvious over Brewer et al. (U.S. Patent No. 3,886,132), for reasons of record. Office Action at pages 3-4. Applicants respectfully traverse this ground for rejection.

Claims 31-34 were rejected under 35 U.S.C. § 103 as being allegedly unpatentable over Breyel et al. ("Synthesis of Mature Human Parathyroid Hormone in *Escherichia coli*,"

3rd Eur. Cong. Biotechnol., *3*:363-369 (1984)) or Sung et al. ("Hybrid Gene Synthesis: Its Application to the Assembly of DNA Sequences Encoding the Human Parathyroid Hormones and Analogues," *Biochem. Cell. Biol.*, *64*:133-138 (1986)) or Mayer et al. (EP 0 139 076) or any reference of the three in view of Kaisha et al. (GB 2 092 596). Applicants respectfully traverse this ground for rejection.

1. Summary of the Cited References

Brewer et al. is directed to isolation and purported purification of hPTH (1-84) from human parathyroid tissue. The reference does not teach the recombinant production of hPTH.

Breyel et al. is directed to expression of mature parathyroid hormone (1-84 amino acids) in *E. coli* under control of a lac-promoter and a trp-promoter. *See* page 363, "Summary," of Breyel et al.

Sung et al. is directed to the production of recombinant vectors containing hPTH DNA. Expression of hPTH is not taught or described.

Mayer et al. is directed to the alleged production of crude extracts of hPTH in prokaryotic and eukaryotic cells (but not yeast).

Kaisha et al. is directed to a process for producing hPTH. This reference does not teach the production of recombinant hPTH, nor does this reference suggest any methods of making recombinant hPTH in microorganisms.

2. The Claimed Invention is Not Taught or Suggested by the Cited References

The cited references do not teach or suggest Applicants' claimed invention, as amended, as they do not teach or suggest, either alone or in combination: (1) a modified form of recombinant hPTH, which is resistant to degradation; (2) recombinant hPTH made using microorganisms comprising a leader sequence having a modified sequence for *Saccharomyces* MFα1; (3) recombinant hPTH made using microorganisms comprising an optimized consensus signal sequence or an optimized functional signal sequence. This is significant as these aspects of the claimed invention provide more efficient and improved compositions of hPTH or hPTH derivatives. For example, the claimed products can have greater than 95% purity (page 5, lines 19-22), and can be produced in quantities of "up to 10 mg/L" (page 6, lines 16-21, of the application). Moreover, some compositions of the claimed

invention can be produced in increased yields of 5 to 10-fold over prior art compositions. *See* page 17, lines 7-11, of the application. This is in contrast to, for example, the hPTH yield observed by Breyel et al. of 140 µg/L and 200 µg/L. *See* page 363, "Summary," of Breyel et al.

Because Applicants' claimed invention is not taught or suggested by the cited references, withdrawal of these grounds for rejection are respectfully requested.

V. CONCLUSION

Applicants respectfully request reconsideration and reexamination of the present application in view of the above amendments and remarks. This application is now in condition for allowance and early notice to that effect is respectfully solicited.

Should the Examiner have any questions or comments regarding the pending application or this Amendment, the Examiner is requested to call the undersigned at 202-672-5538.

If there are any fees due in connection with the filing of this Amendment, please charge the fees to our Deposit Account No. 19-0741. If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit Account.

Respectfully submitted,

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Dated: Oct 23, 1998

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